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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Donald W. Petersen

Art Unit : 1651

Serial No. : 10/060,697

Examiner : Jean C. Witz

Filed : January 30, 2002

Title : BONE GRAFT SUBSTITUTE COMPOSITION

Commissioner for Patents
Washington, D.C. 20231

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RESPONSE TO ACTION MAILED JULY 2, 2002

Claims 16-30 (attached), of which claims 16 and 27 are in independent form, are presented for examination. Claims 16-26, for example, cover a bone graft substitute composition including calcium sulfate, demineralized bone matrix, cancellous bone, a plasticizing substance, and a mixing solution.

The Examiner has rejected claims 16-30 under 35 U.S.C. § 103(a) are being unpatentable over the combined teachings of U.S. Patent No. 5,484,601 (O'Leary), U.S. Patent No. 5,385,887 (Yim), and WO 98/40113 (Wironen) taken as a whole. What the Examiner has actually done, however, is picked and chosen, at the Examiner's convenience, components from three distinct compositions described in three references and then combined them to reconstruct the compositions covered by the claims using hindsight. In particular, the Examiner has picked calcium sulfate from Yim, picked demineralized bone matrix, a plasticizing substance, and a mixing solution from O'Leary, and picked cancellous bone from Wironen. The Examiner has reasoned that since the components are "conventional" and "well known", then it is proper to combine the components in the manner required by the claims. But this is an inappropriate basis for a rejection based on 35 U.S.C. § 103(a).

First, Applicant does not dispute that the components required by the claims are known and have been used in other compositions. However, the fact that the components could be

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removed from the other compositions and combined to obtain the claimed compositions is not a sufficient basis for obviousness. There must be some suggestion in the cited references to form the specific combination of components required by the claims.

Second, while the Examiner claimed to have considered the references as a whole, the Examiner has actually ignored aspects of the references that suggest away from the Examiner's combination. Indeed, if the references were taken as a whole, as suggested by the Examiner, then one skilled in the art would not be motivated to combine the references.

For example, one skilled in the art reading Wironen would be discouraged from looking to O'Leary. Wironen expressly characterizes O'Leary but states:

Thus, one commercially available product, GRAFTON®, (see U.S. Patent No. 5,484,601) is a **non-cross-linkable composition** of demineralized bone powder suspended in a polyhydroxy compound (e.g. glycerol) or esters thereof, optionally including various other ingredients, including gelatin. It is considered likely that this material is **rapidly washed away from the implant location** as the carrier matrix is glycerol, which is water soluble.¹

This characterization of O'Leary (U.S. 5,484,601) is directly contrary to Wironen's explicit disclosure that "there is a need for a product which does not allow for particle migration" and that "the thermal cross-linking property [of the carrier is] so important to the composition of this [Wironen's] invention."² Indeed, Wironen discloses glycerol as a neurolytic agent, while O'Leary discloses that glycerol is the "especially preferred" carrier.³ Thus, taken as a whole, one skilled in the art reading Wironen would not be motivated to look to O'Leary, let alone combine O'Leary with Wironen.

With regard to combining Wironen with Yim, Wironen discloses using a gelatin as a carrier that has the ability to thermally cross-link.⁴ As noted above, Wironen considers this thermal cross-linking property to be "important" to his composition. But neither Wironen nor Yim discloses or suggests that calcium sulfate is a carrier that has the ability to thermally cross-

¹ Wironen p. 3, l. 22-26, emphasis added.

² Wironen p. 3, l. 2-4; p. 8, l. 21-22.

³ Wironen Fig. 1; and O'Leary col. 3, l. 49-52.

⁴ Wironen p. 8, l. 14-15.

link. Thus, there is no suggestion or motivation to combine calcium sulfate with the cancellous bone of Wironen.

What is more, one skilled in the art would not be motivated to combine the calcium sulfate of Yim with O'Leary's composition because the reasons that Yim discloses for adding calcium sulfate are either inconsistent with the type of compositions that O'Leary intended to form or that the reasons have already been addressed by O'Leary.

O'Leary describes flowable demineralized bone powder compositions capable of having widely varying consistency. As specifically defined by O'Leary, the term "flowable"

applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams and fillers.⁵

To provide a flowable material, O'Leary combines the bone powder with a liquid synthetic organic material, e.g., glycerol, that functions as a carrier or suspension agent.⁶ In cases where the composition can quickly or prematurely separate from the carrier or settle out from the composition such that application of the composition is difficult or inconvenient, O'Leary discloses adding a thickener, such as polyvinyl alcohol or a cellulosic material, to change the thixotropic and suspension-keeping characteristics (e.g., consistency) of the composition.⁷

Yim discloses adding calcium sulfate to a composition to improve retention of the composition at a wound site, to reduce formulation setup time, to improve osteoconduction, to reduce preparation time, to improve moldability and handling characteristics, and to improve consistency.⁸ As mentioned above, these reasons for adding calcium sulfate are either inconsistent with the type of compositions that O'Leary intended to form or have already been addressed by O'Leary.

For example, improving retention of the composition at the wound site and reducing formulation setup time suggest that the composition should be relatively viscous (so that it could

⁵ O'Leary col. 3, l. 30-36.

⁶ *Id.* col. 3, l. 15-20.

⁷ *Id.* col. 3, l. 55 - col. 4, l. 6.

⁸ Yim col. 2, l. 51-65; and col. 7, l. 50-59.

be retained) in a relatively short time (i.e., reduced setup time). However, as clearly defined by O'Leary, in some embodiments, the compositions are intended to be "runny," which suggests relatively low viscosity and relatively long setup time. In embodiments where O'Leary's compositions are intended to be like a putty (e.g., for improved retention and setup time), O'Leary disclosed adding a thickener such as a cellulosic material. One skilled in the art would not be motivated to further add Yim's calcium sulfate because that would be unnecessarily redundant, and as a result, there is no motivation to form Applicants' claimed composition.

Furthermore, O'Leary already addressed all the other reasons Yim disclosed for adding calcium sulfate. For example, O'Leary addressed improved osteoconduction by disclosing that glycerol is a preferred carrier because it "exhibits a particularly pronounced capability for dissolving osteogenic proteins present in the bone powder and enhancing the availability of these proteins at the bone repair site."⁹ Yim, however, does not disclose that calcium sulfate improves osteoconduction when used as a carrier for a material such as demineralized bone. O'Leary addressed reduced preparation time by disclosing that the carrier includes organic materials that are flowable liquids at ambient temperatures to provide a flowable material of widely varying consistency; on the other hand, calcium sulfate is a powder to which a solubilizing liquid is added, which can increase preparation time. As discussed above, O'Leary expressly disclosed the compositions as being handle-able and moldable ("shape-sustaining but readily deformable"), as well as having improved consistency (the consistencies range, e.g., from "those which behave like putty to those which are runny"). O'Leary explicitly disclosed that a thickener can be added to make the composition easier and more convenient to apply. Therefore, since O'Leary addressed all of Yim's reasons for adding calcium sulfate, one skilled in the art would not be motivated to further add the calcium sulfate. In other words, there is no teaching, suggestion, or incentive to make the combination as suggested by the Examiner.

Moreover, one skilled in the art reading Yim would not be motivated to combine demineralized bone to Yim's composition. Yim disclosed compositions wherein osteogenic proteins are utilized in the form of a pharmaceutically acceptable *solution* (including reconstitution from a lyophilized form). In particular, Yim disclosed that

⁹ O'Leary col. 3, l. 49-52.

It is optimal to solubilize the osteogenic protein at concentrations of at least about 1 mg/ml, preferably about 2 to 8 mg/ml, so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary.¹⁰

Yim further disclosed that to prevent formation of particulates, a non-ionic surfactant can be added to the composition.¹¹

One skilled in the art reading Yim would not be motivated to add demineralized bone material (a source of osteogenic proteins) to Yim's compositions. Demineralized bone is not in the form of a pharmaceutically acceptable solution. Instead, demineralized bone is formed as *solid particles*, which Yim expressly wanted to eliminate. Thus, one skilled in the art reading Yim would not be motivated to combine demineralized bone matrix to Yim's composition.

Reading the references as a whole, as suggested by the Examiner, one skilled in the art would not be motivated to combine the references. The Examiner has arbitrarily picked and chosen what is convenient to reconstruct Applicant's claimed compositions, while ignoring aspects of the references that discourages such a reconstruction. The rejection, therefore, is clearly based on improper hindsight reasoning and should be withdrawn.

Applicant believes the claims are in condition for allowance, which action is requested.

¹⁰ Yim col. 3, l. 34-39 (emphasis added).

¹¹ *Id.* col. 4, l. 2-7.

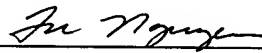
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Attorney's Docket No.: 06317-038003

Enclosed is a Petition for Extension of Time with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: January 2, 2003



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